REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1-40 are pending.

In order to advance prosecution in this application, the claims have been amended to specify that one or more ADP-ribosylating exotoxins are used as an adjuvant or other immunostimulant.

The amendments to the claims are supported by the original disclosure and, thus, no new matter has been added. But if the Examiner should disagree, she is respectfully requested to point out the challenged limitation with particularity in the next Office Action so support may be cited in response.

A clean copy of the declaration and power of attorney submitted in the parent Appln. No. 08/896,085 is attached in response to the Examiner's requirement for a new declaration.

The title has been made more descriptive of the claimed invention.

A substitute Form PTO-1449 is attached. Please use the attached in lieu of the previously submitted Form PTO-1449 that have been made of record. It is urged that use of the attached Form PTO-1449 will reduce possible confusion by the printer when this information is listed on the front of a patent because it represents an updated and consistent format for the references considered by the Examiner. Any references not submitted in this application were submitted to or cited by the Examiner in US 5,910,306; US 5,980,898; or related U.S. Appln. Nos. 08/749,164; 08/896,085; 09/157,395; 09/257,188; 09/309,881; 09/311,720; 09/316,069; 09/337,746; 09/545,417; and 09/585,559. The Examiner may wish to consider these related patent file wrappers and applications in prosecution of this application.

35 U.S.C. § 112 - Definiteness

Claims 4-6 were rejected as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

Claim 4 has been amended to clarify that the penetration enhancer is used to enhance the immune response induced by the formulation through penetration of the organism's formerly intact skin.

Claims 5-6 do not lack antecedent basis. The phrases cited on page 3 of the Action do not require antecedent basis because they are not preceded by "the" or "said" (i.e., a definite article). They further limit independent claim 1 from which the dependent claims depend.

Applicants request withdrawal of this claim rejection made under Section 112, second paragraph, because the pending claims are clear and definite.

35 U.S.C. § 102 - Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claim. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1-4, 7-12, 18-21, 30 and 21-35 were rejected under Section 102(b) as being allegedly anticipated by Domb (US 5,340,588). Applicants traverse because all limitations of the claimed invention are not taught by the cited reference.

The claims require the use of an ADP-ribosylating exotoxin. Domb does not teach or suggest using ADP-ribosylating exotoxin to induce an immune response by transcutaneous immunization. Thus, the cited reference does not anticipate the claimed invention.

Applicants respectfully submit that this Section 102 claim rejectionshould be withdrawn.

35 U.S.C. § 103 – Nonobviousness

To establish a case of *prima facie* obviousness, all claim limitations must be taught or suggested by the prior art. See M.P.E.P. § 2143.03. Obviousness can only be established by combining or modifying the prior art teachings to produce the claimed invention if there is some teaching, suggestion, or motivation to do so found in either the references themselves or in the knowledge generally available to a person of ordinary skill in the art. See, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Jones*, 21 USPQ2d 1941, 1943-44 (Fed. Cir. 1992). It is well established that the mere fact that references <u>can</u> be combined does not render the

resultant combination obvious unless the desirability of that combination is also taught or suggested by the prior art. See *In re Mills*, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990). Thus, even if all elements of the claimed invention were known, this is not sufficient by itself to establish a *prima facie* case of obviousness without some evidence that supplies the impetus to combine those teachings in the manner proposed by the Examiner. See *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (B.P.A.I. 1993).

Evidence of the teaching, suggestion or motivation to combine or to modify references may come explicitly from statements in the prior art, the knowledge of a person of ordinary skill in the art or the nature of the problem to be solved, or may be implicit from the prior art as a whole rather than expressly stated in a reference. See *In re Dembiczak*, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); *In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000). Rigorous application of this requirement is the best defense against the subtle, but powerful, attraction of an obviousness analysis based on hindsight. See *Dembiczak* at 1617. Whether shown explicitly or implicitly, however, broad conclusory statements standing alone are not evidence because the showing must be clear and particular. See *id.*

Finally, a determination of *prima facie* obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-12, 16-23, and 29-35 were rejected under Section 103(a) as allegedly unpatentable over Domb or alternatively over Paul et al. (1995) and further in view of Marinaro et al. (1995) and "the admitted prior art" on page 16 of this specification. Applicants traverse.

Paul teaches away from the claimed invention which requires use of one or more ADP-ribosylating exotoxins. Paul uses transferosomes for immunization with an antigen. Paul does not use an adjuvant or any other immunostimulant. Thus, a person of ordinary skill in the art would not have been motivated to use one or more ADP-ribosylating exotoxins to induce an immune response. There is no teaching or suggestion by Paul that use of an adjuvant or other immunostimulant would be beneficial. Without such a teaching or suggestion, why would a person of ordinary skill in the art be motivated to modify Paul by using an ADP-ribosylating exotoxin as an immunostimulant? The evidence of record does not provide the motivation.

Marinaro and "the admitted prior art" discussed in this specification were cited for disclosing that cholera toxin and its B subunit were known to be adjuvants. While they were known as adjuvants, the cited references and the evidence of record is devoid of any teaching or suggestion that one or more ADP-ribosylating exotoxins could be used as an adjuvant or immunostimulant for transcutaneous immunization (i.e., topical or epicutaneous application to intact skin). Without providing such evidence, a reasonable expectation of success has not been established because the route of administration required by the claimed invention is different from the mucosal, enteral, or parenteral routes described in the prior art. Why would a person of ordinary skill in the art have had a reasonable expectation of success in inducing an immune response applying ADP-ribosylating exotoxin to intact skin with or without penetration enhancement?

Claims 1-12, 16-24, and 27-35 were rejected under Section 103(a) as allegedly unpatentable over Domb or alternatively over Paul et al. (1995) in view of Kosecka (1994) and "the admitted prior art" on page 16 of this specification and in further view of Wille et al. (US 5,686,100). Applicants traverse.

Kosecka and "the admitted prior art" discussed in this specification were cited for disclosing that pertussis toxin, cholera toxin, and its B subunit were known to be adjuvants. While they were known as adjuvants, the cited references and the evidence of record is devoid of any teaching or suggestion that one or more ADP-ribosylating exotoxins could be used as an adjuvant or immunostimulant for transcutaneous immunization (i.e., topical or epicutaneous application to intact skin). Without providing such evidence, a reasonable expectation of success has not been established because the route of administration required by the claimed invention is different from the mucosal, enteral, or parenteral routes described in the prior art. Why would a person of ordinary skill in the art have had a reasonable expectation of success in inducing an immune response applying ADP-ribosylating exotoxin to intact skin with or without penetration enhancement?

Finally, the use of ADP-ribosylating exotoxins is unexpectedly superior to the use of other adjuvants and immunostimulants in transcutaneous immunization. The cited references and evidence of record do not show this preference for using one or more ADP-ribosylating exotoxins instead of other adjuvants or immunostimulants.

Thus, the prior art does not show the desirability of using one or more ADP-ribosylating exotoxins as an adjuvant or other immunostimulant in transcutaneous immunization or that such large molecules would effectively penetrate skin to induce an immune response. For these reasons, Applicants respectfully submit that these Section 103 claim rejections should be withdrawn.

Double Patenting

Claims 1-4, 6-12, 16-21 and 27-35 were rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12 and 15-29 of US 5,910,306 in view of Unger (US 5,733,572) and in further view of Albert (US 5,256,422.

Upon an indication that the claims are allowable, Applicants will submit a terminal disclaimer. To do so at this time before an indication that the claims are otherwise allowable, would unduly prejudice Applicants by requiring submission of the Official fee for a terminal disclaimer before there was any certainty that a patent would issue. Such payment would be wasted if the claims stood rejected.

Conclusion

Having fully responded to the objections and rejections in the pending Office Action (Paper No. 14), Applicants urge that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if further information is needed.

Respectfully submitted,

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APPENDIX

MARKED-UP VERSION TO SHOW CHANGES

IN THE TITLE:

The title is amended as follows.

ADP-RIBOSYLATING EXOTOXIN USED [ADJUVANT] FOR TRANSCUTANEOUS IMMUNIZATION

IN THE CLAIMS:

The claims are amended as follows.

1. (Amended) A method of inducing an immune response comprising:

(a) applying a formulation to intact skin of an organism, wherein the formulation comprises an antigen and an ADP-ribosylating exotoxin [adjuvant];

(b) activating a Langerhans cell with the ADP-ribosylating exotoxin [adjuvant]; and

(c) presenting the antigen on a cell surface of the Langerhans cell to a lymphocyte, thereby inducing the immune response in the organism.

2. (Amended) The method of claim 1, wherein the formulation consists essentially of antigen and ADP-ribosylating exotoxin [adjuvant].

4. (Amended) The method of claim 1[, wherein] further comprising use of a physical, chemical, electrical, or sonic penetration enhancer to enhance said immune reponse by penetrating said organism's skin.

20. (Amended) The method of claim 1, wherein the ADP-ribosylating exotoxin [adjuvant] activates the Langerhans cell.

21. (Amended) The method of claim 1, wherein the ADP-ribosylating exotoxin [adjuvant] enhances antigen presentation to a lymphocyte.

22. (Amended) The method of claim 1, wherein the [adjuvant is an] ADP-ribosylating exotoxin is pertussis toxin or a toxoid derivative thereof.

23. (Amended) The method of claim 22, wherein the ADP-ribosylating exotoxin [adjuvant] is cholera toxin (CT) or cholera toxin B subunit (CTB) or a toxoid derivative thereof.

24. (Amended) The method of claim 22, wherein the ADP-ribosylating exotoxin [adjuvant] is *E. coli* heat-labile enterotoxin (LT) or a toxoid derivative thereof [or pertussis toxin].

25. (Amended) The method of claim 22, wherein the ADP-ribosylating exotoxin [adjuvant] in the formulation is provided as a nucleic acid encoding [an] ADP-ribosylating exotoxin.

30. (Amended) A method of immunization comprising applying a formulation to intact skin of an organism, wherein the formulation consists essentially of one or more ADP-ribosylating exotoxins [comprises an antigen and an adjuvant].

32. (Amended) A method of inducing an immune response comprising:

(a) applying a formulation to intact skin of an organism, wherein the formulation comprises an antigen and an ADP-ribosylating exotoxin [adjuvant];

(b) activating an antigen presenting cell with the ADP-ribosylating exotoxin [adjuvant]; and

(c) presenting the antigen on a cell surface of the antigen presenting cell to a lymphocyte, thereby inducing the immune response in the organism.

36. (Amended) A method of inducing an immune response to an antigen comprising:

(a) applying a formulation to intact skin of an organism, wherein the formulation comprises (i) a nucleic acid containing a sequence encoding the antigen and (ii) an ADP-ribosylating exotoxin [adjuvant]; and

(b) inducing the immune response in the organism without perforating the skin, wherein the immune response is specific for the antigen.

37. (Amended) The method of claim 36, wherein the formulation consists essentially of nucleic acid and one or more ADP-ribosylating exotoxins [adjuvant].